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EDITORIAL

# Understanding Pancreatic Ductal Morphogenesis and Function: Gene Deletion Is Only the Beginning

The mammalian pancreas arises as endodermal buds from the foregut that undergo branching morphogenesis, resulting in distinct acinar, ductal, and islet cell components. This differentiation is largely driven by ordered expression of distinct transcription factors. Of the three cell types, the least is known about the factors specifying ductal cells. In the current issue of *Cellular and Molecular Gastroenterology and Hepatology,* Ferreira et al[1] add to the list of transcription factors specifying duct cells by showing that the hematopoietic-expressed homeobox protein (Hhex) is located in duct cells and is required for maintenance of the neonatal pancreas. Hhex is required for the development of heart and organs derived from foregut endoderm. Gene deletion results in embryonic lethality. Prior genomewide association studies have linked Hhex to diabetes; in a study focused on pancreatic islets, Zhang et al[2] found Hhex protein to be localized also in pancreatic duct cells. In the present study, this group shows that Hhex was expressed in all ductal cells throughout development and in postnatal and adult pancreas.[1]

As an important initial step, the authors deleted Hhex specifically in the pancreas. To do this they used mice with floxed *Hhex* genes and two distinct Cre drivers: Pdx-1 $Cre^{Early}$ and Sox9-$CreER^{T2}$. Pdx-1 Cre, which is known to be expressed in all cells of the developing pancreas, induced a chronic pancreatitis phenotype beginning at postnatal day 3. The authors focus on ductal abnormalities described as ectasia, in which the ducts are enlarged, tortuous, and filled with eosinophilic proteinaceous material. However, all the hallmarks of chronic pancreatitis were present, including inflammation, fibrosis, acinar cell loss, and acinar-to-ductal metaplasia. In the second model they used Sox9 CreER to delete Hhex specifically in ductal cells that express Sox 9 in the adult pancreas (9–12 weeks of age). However, using this Cre there was no change in duct morphology or pancreatitis parameters. The authors concluded that Hhex was not required for the maintenance of the ductal tree in adult mice.

Often when gene deletion leads to a negative pancreatic phenotype, the investigators study the response of the pancreas to tissue injury by inducing pancreatitis, typically using the caerulein hyperstimulation experimental model. The pancreatitis may be reduced or accentuated, or pancreatic regeneration may not occur. This could be especially interesting for the study of the function of Hhex. The authors, however, turned their attention to the equally interesting question of the mechanism of the pancreatitis that developed when Hhex was deleted during embryogenesis, and they asked whether Hhex regulated the genes known to specify duct function such as Hnf6, Hnf1$\beta$, and the genes necessary for primary cilia formation. None of these genes were affected by Hhex ablation.

At this point, the authors propose that Hhex may regulate genes involved in duct cell function, and they suggest that the pathologic changes closely resemble a report in which pancreatic ductal hypertension was induced in rats by ductal cannulation and elevation of the outflow.[3] This is difficult to assess however, because the morphologic findings of pancreatitis are often nonspecific, as is pancreatic stellate cell (PSC) activation as a marker of increased duct pressure. Thus but further experiments will be necessary to fully categorize these processes.

The question of whether ductal hypertension is a part of chronic pancreatitis in human disease is also controversial. Nevertheless, based on the data in hand, the authors sought a gene with altered expression that could lead to enhanced secretion, which in the presence of small ducts in young mice could induce ductal hypertension. They focused on Natriuretic peptide receptor 3 (Npr3) because it showed a 4.7-fold increase in mRNA in duct cells from Hhex ablated mice and also an increase in Npr3 immunostaining. Overexpression of Hhex in duct cells reduced Npr3 levels. Although there is some evidence that Npr3 can affect pancreatic secretion, future experiments will be necessary to prove this point conclusively and show that in the presence of increased Npr3 the normal postnatal secretion of gastrointestinal hormones such as cholecystokinin and secretin will induce pancreatitis.

The authors are to be congratulated on this study. It clearly puts Hhex on the pancreas development map and shows it to be worthy of further study. Because Pdx-1 Cre is expressed outside as well as inside the pancreas, future studies might involve a more specific Cre driver. Could Sox9 Cre or a carbonic anhydrase Cre expressed at its natural time in embryogenesis be used? Further studies of the function of Hhex could include studying the function of duct cells in cannulated or cultured ducts to analyze the function of specific molecular components and the use of small-interfering RNA to acutely regulate transport protein expression. I look forward to learning more about Hhex, an interesting new player in the pancreatic ducts.

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**Conflicts of interest**
The author discloses no conflicts.

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